Genital Ulcer Disease

Herpes simplex virus, Treponema pallidum, Haemophilus ducreyi

What is Genital Ulcer Disease?

- Genital ulcer disease is an ulcerative, erosive, pustular or vesicular genital lesion(s), with or without regional lymphadenopathy, that may be caused by a number of sexually transmitted infections (STIs) and non–STI-related conditions.
- Noninfectious causes of genital ulcers may include trauma, psoriasis, inflammatory diseases, bad reactions to skin care products and fixed drug eruptions.
- In the United States, the most common causes of genital ulcer disease includes genital herpes, syphillis and chancroid.
- As reported by the Centers for Disease Control and Prevention (CDC) in their 2015 Sexually Transmitted Disease Treatment Guidelines, the frequency of each condition differs by geographical area and population; however, genital herpes is the most prevalent of these diseases (20).
- Medical Diagnostic Laboratories (MDL) offers a panel of testing for the three most common causes of genital ulcer disease in the United States utilizing the ***OneSwab***® and ThinPrep® specimen collection platforms. **Test 115: Genital Ulcer Disease Panel (HSV-1 & HSV-2, *H. ducreyi, T. pallidum*) by Real-Time PCR.**

Herpes simplex virus (HSV)

Epidemiology

Herpes simplex virus has been recognized in medicine for centuries. Cold sores were described in ancient Roman medical texts in 100 AD and genital herpes was described in a treatise on venereal disease in 1754 (2). HSV infection is common in all groups in the United States. Since the late 1970's, the incidence of infection has increased 30% (1). It is estimated that 45 million Americans are infected with genital herpes and that 500,000 new cases occur in the US each year (1, 3). Infection with HSV-1 is acquired more frequently than HSV-2. More than 90% of adults in the US have antibodies against HSV-1 by their fifth decade of life (2). HSV infection occurs more frequently in women than in men. It has been documented that 30% of the female population in the US harbors HSV-2 (3, 4). The lifetime incidence of HSV-2 infection in various groups has been documented as follows; white women: 25%, white men: 20%, African American women: 80%, African American men: 60% (2). Risk factors for genital herpes include age, years of sexual activity, race, one or more episodes of other genital infections, decreased annual family income, and multiple sex partners (4).

Pathogenesis

Herpes simplex virus belongs to the family Herpesviridae. This family is made up of eight human herpes viruses which are subdivided into three classes. The alpha class is made up of HSV-1, HSV-2, and Varicella-Zoster virus. HSV-1 and HSV-2 are both double-stranded DNA viruses with an icosahedral capsid and a lipid envelope. The virus gains entry through contact with mucus membranes or small abrasions in the epidermis. Replication begins at the port of entry. The virus then travels through the axon to the dorsal root ganglion of nerves of the spinal cord where it enters a latent state. This process of latency makes HSV infection chronic and lifelong. During latency, viral genomes are maintained in a repressed state allowing infected cells to continue to survive and function normally. Various stimuli can cause reactivation of the virus, including immunosuppression, trauma to the skin or ganglia, cold, fever, intense sunlight, emotional stress, or menstruation (2, 4). Viral activation results in replication and release from the neuron into the surrounding epithelial cells where viral replication continues. Due to migration of the virus along the peripheral sensory nerves, it can spread over large areas. Immunocompromised individuals typically have more severe and prolonged periods of reactivation which may be due to alterations in cellular immunity. In particular, T-cells have a strong role in viral containment and are crucial in preventing lethal disseminated disease. It has been well documented that HSV-2 increases the risk of acquiring HIV (2).

Clinical Significance

Herpes simplex virus produces a wide spectrum of clinical disease, ranging from mucocutaneous lesions to disseminated disease which may be life threatening in a subset of patients. The incubation period for infection is typically 2 to 14 days. HSV-1 and HSV-2 are transmitted through close contact with an infected person that is actively shedding the virus from mucus membranes or in genital or

oral secretions. It is estimated that the susceptible sexual partners of males with active lesions of the genitalia will develop infection following 50% to 90% of exposure incidents (4).

Genital HSV infection typically progresses in three stages. The first stage, primary infection, is the initial infection with either HSV-1 or HSV-2 without prior exposure to the other. This stage usually persists for 15 days including 12 days of active viral shedding. It is typically accompanied by systemic symptoms such as fever, lymphadenopathy, malaise, myalgia, headache, and nausea and is characterized by multiple, large, painful lesions which begin as vesicles with a clear fluid. Vesicles progress to pustules which rupture producing shallow, painful, erythematous ulcers covered by ragged white membranes. It is also common for a primary infection to cause cervical ulcers in women. Local symptoms may include itching, dysuria, vaginal and urethral discharge, and inguinal lymphadenopathy. The cervix and urethra are involved in 80% of women with initial episodes of infection (2). Frequently, extragenital lesions of the buttocks, thigh, groin, finger or eye are also observed. With HSV-2, 29% of extragenital lesions will occur on the buttocks and in HSV-1, 25% will occur in or around the mouth (2). However, most HSV infections occur subclinically, without symptoms. Some studies indicate that only 20% to 25% of people with HSV-1 and 10% to 20% of people with HSV-2 report oral-labial or genital lesions (2).

The second stage of genital HSV infection, recurrent infection, is a reactivation of latent infection and not a re-infection. Reactivation is typically preceded by 1 to 2 days of prodromal symptoms which may include mild localized tingling, itching or pain. This stage typically lasts for 7 days, with 5 days of viral shedding. The lesions are typically fewer in number and smaller in size compared to those observed during primary infection. Recurrence of infection occurs more often with HSV-2 than HSV-1 infection. Within 6 months of a primary infection, 50% of patients will experience a recurrence (1). Within 12 months of the initial episode of infection, 80% of HSV-2 and 55% of HSV-1 infections will have reactivated (1). HSV-1 infection is more likely to reactivate in oral presentations while HSV-2 infections are 8 to 10 times more likely to reactivate in genital infection (2).

In a non-primary first episode, a patient that experiences a clinical or subclinical episode with either HSV-1 or HSV-2 has already had prior exposure to the other subtype. A subclinical infection occurs in the absence of any lesions, symptoms, or other indication of infection. One crucial feature of HSV infection is the phenomenon of asymptomatic viral shedding which is the cause of the majority of sexual and vertical transmissions. In asymptomatic viral shedding, active, infectious virus can be detected in the genital or urinary tract of women and men in the absence of any lesions or outward sign of infection. In women, common sites for viral shedding are the cervix, vulva, anus, and urethra. In men, viral shedding occurs from penile skin, urethra, anus, and occasionally semen. Women with frequent recurrences of infection have more frequent episodes of viral shedding. In the 6 months following acquisition of a primary infection, subclinical HSV reactivation is more likely. During this period, the virus can be detected by PCR in 2% to 45% of days which decreases over time (2). Persons infected for 5 to 10 years are half as likely as people infected for less than 2 years to have subclinical viral shedding (2).

HSV infection can greatly impact pregnancy and the neonate. The neonate can acquire infection during pregnancy, delivery, or immediately following birth. Neonatal HSV is acquired during delivery in 90% of cases, congenitally in 5% to 8% of cases, and in a few cases transmission has been documented post-natally (2). Viral shedding from an infected mother's cervix is associated with an increased risk for neonatal transmission (1). Again, subclinical viral shedding plays an important role. More than 70% of infants infected with HSV are born to mothers with no signs or symptoms of lesions during delivery (2). The risk of transmission to the neonate varies depending upon the clinical stage of the mother's infection. The risk of transmission from a mother during primary infection is 50% compared with 20% during recurrent HSV-2 infection (2). There is also an increased risk of neonatal transmission if HSV infection is acquired later in pregnancy near the time of labor (2). The impact of HSV infection in neonates can be devastating. Infected neonates are more likely to experience central nervous system (CNS) involvement and disseminated infection. If left untreated, 70% will develop CNS involvement, 65% will die, and less than 20% with CNS involvement will continue to develop normally (2).

HSV infection can also manifest in other clinical conditions. Herpetic Whitlow is a cutaneous infection usually affecting the finger or thumb. This disease is an occupational hazard for dentists, physicians, and other health care workers. Infection often occurs at the site of previous minor trauma or breaks in the skin. Vesicles develop which eventually rupture to form ulcers as well as edema, erythema, and pain. Individuals with Herpetic Whitlow may also experience fever, chills, and lymphadenopathy. This occurrence usually persists for 10 to 14 days and then subsides. HSV infections of the eye are the most common cause of corneal blindness in the US (2). In cases of acute, sporadic viral encephalitis,10% to 20% are also caused by HSV infection (2). Disseminated infection can occur with multiple vesicles rupturing to form lesions

over a widespread area of the trunk and extremities. Other visceral organs may be affected, developing into hepatitis, pneumonitis, and arthritis (2).

Diagnosis

Due to the asymptomatic nature of many infections and the fact that many lesions when present are atypical, including fissures, furuncles, excoriations, and nonspecific vulvar erythema, laboratory diagnosis is crucial (1, 2). Traditionally, cell culture has been utilized for HSV detection. Clinical specimens are inoculated into a cell monolayer and allowed to grow for several days. The cells are then analyzed microscopically for discernable cytopathic effects of the virus including large multinucleated cells containing eosinophilic intranuclear inclusion bodies. The maximum sensitivity of this assay is only 60% to 70% (3, 4). Due to the inherent difficulties associated with culturing the virus, there is a false negative rate which varies from 5% to 30% (1).

The Papanicolaou and Zanck smears consist of collecting samples from lesions, smearing them on a glass slide, and analyzing the stained slides for characteristic cellular changes such as intranuclear inclusions and multinucleated giant cells. The sensitivity of these methods are only 50% and are therefore not recommended (1, 3). Antigen detection systems typically utilize monoclonal antibodies directed against certain markers (antigen) found on the surface of HSV infected cells. These assays have limited diagnostic use due to their limited sensitivities of 73.8%, particularly in asymptomatic viral shedding and healing lesions (5). Traditional immunofluorescent and ELISA assays are also available; however, due to frequent cross-reactivity between the two subtypes, they should not be used to diagnose acute infection. The reported sensitivity of these assays are both approximately 80% (3). The newer serological type-specific IgG–based assays can distinguish between HSV-1 and HSV-2. Most use purified glycoproteins such as gG1 and gG2 which are distinct between the two subtypes. Although their sensitivity is greater than 80%, false negatives can occur early in infection (4).

Table 1. Sensitivities for HSV detection tests.

Method	Sensitivity
Cell Culture	60% - 70%
Pap & Zanck Smears	50%
Antigen Detection Systems	73.8%
Immunofluorescent & ELISA Assays	80%
Type Specific IgG-based Assays	>80%
Polymerase Chain Reaction (PCR)	100%

The most sensitive diagnostic technique currently available is PCR (1). The recent advent of Real-Time PCR technology allows for the detection of PCR amplification while the reaction is proceeding. Conventional PCR methods only allow the visualization of product at the end of the reaction, or end-point analysis. In addition to the highly specific primers that are used in a PCR reaction, Real-Time PCR utilizes a probe to enhance both the sensitivity and specificity of the assay.

Recommendations

The Association for Genitourinary Medicine (AGUM) and the Medical Society for the Study of Venereal Disease (MSSVD) published national guidelines for the management and treatment of genital herpes (6). Recommendations from the Centers for Disease Control and Prevention (CDC) for the treatment and management of patients can also be found in Morbidity and Mortality Weekly Report (MMWR), Vol. 64 pages 27-33.

Table 2. Treatment Recommendations. CDC's 2015 Sexually Transmitted Diseases Summary of 2015 CDC Treatment Guidelines Pocket Guide (20).

Recommended Regimens For First Clinical Episode of Genital Herpes
Acyclovir 400 mg orally three times a day for 7-10 days [b] ***OR***
Acyclovir 200 mg orally five times day for 7-10 days [b] ***OR***
Valacyclovir [a] 1 g orally twice a day for 7-10 days [b] ***OR***
Famciclovir [a] 250 mg orally three times a day for 7-10 [b] days
Episodic Therapy For Recurrent Genital Herpes
Acyclovir 400 mg orally three times a day for 5 days ***OR***
Acyclovir 800 mg orally two times a day for 5 days ***OR***
Acyclovir 800 mg orally three times a day for 2 days ***OR***
Valacyclovir [a] 500 mg orally twice a day for 3 days ***OR***
Valacyclovir [a] 1 g orally once a day for 5 days ***OR***
Famciclovir [a] 125 mg orally twice a day for 5 days ***OR***
Famciclovir [a] 1000 mg orally twice a day for 1 day [b] ***OR***
Famciclovir [a] 500 mg orally once, followed by 250 mg twice a day for 2 days
Recommended Regimens For Suppressive [c] Therapy For Recurrent Genital Herpes
Acyclovir 400 mg orally twice a day ***OR***
Valacyclovir [a] 500 mg orally once a day ***OR***
Valacyclovir [a] 1 g orally once a day ***OR***
Famciclovir [a] 250 mg orally twice a day

[a] No definitive information available on prenatal exposure.

[b] Treatment may be extended if healing is incomplete after 10 days of therapy.

[c] Consider discontinuation of treatment after one year to assess frequency of recurrence.

Treponema pallidum

Epidemiology

Treponema pallidum is the causative agent of the sexually transmitted disease syphilis. Syphilis has been around for centuries. In the US, incidence peaked around 1947 and then dropped with the introduction of penicillin (7). There was a steady decline in the incidence of primary and secondary syphilis from about 1990 to 2000. However, 2001 and 2002 saw an increase by 12.4% (11). In the US, African Americans account for approximately 49.8% of cases (11). There is a heavy concentration of syphilis in the south, which is equally distributed between urban and rural areas. The highest occurrences of syphilis are in women age 20-24 and men age 35-39 (11). Recent outbreaks in the US were associated with crack cocaine use. Certain risk factors include more than four sex partners and a lack of barrier contraceptive (condom) use.

Pathogenesis

T. pallidum is an anaerobic, obligate human bacteria. It is a member of the family Spirochaetaceae. This family is comprised of three genera; Treponema, Borrelia, and Leptospira. Often referred to as spirochetes, they are spiral shaped and move in a rotary, corkscrew, or springing fashion. Most Treponemas are nonpathogenic. Some are found as colonizers of the oral cavity and gastrointestinal tracts of humans. Although they do replicate when inoculated into various small mammals such as rabbits, they have never been grown *in vitro* in the laboratory. The intense cellular immune response elicited by the host, results in inflammation and is thought to be responsible for many of the subsequent clinical manifestations of infection (8). The proteins and lipoproteins that compose the outer membrane as well as antigenic variation enable the organism to evade the host's immune response.

Clinical Significance

T. pallidum is transmitted primarily via sexual contact. It is estimated that 30% (range 10% to 60%) of casual sexual contacts and 90% of steady partners of infectious individuals will acquire this organism (9). It enters the body through small breaks in the skin or abrasions of mucosal surfaces. Typically, there is an incubation period of 10 to 19 days before the primary lesion appears. This lesion, commonly referred to as a chancre, occurs at the point of entry of the spirochete. It is a painless, ulcerated lesion with a raised border and indurated base. In men, this primary lesion is generally readily noticeable and results in diagnosis during this primary stage. However, in women, it usually occurs on the cervix or in the vagina and goes unrecognized. It is rare for females to be diagnosed during this primary stage (9). If untreated, the chancre will resolve within 3 to 6 weeks.

The secondary stage of syphilis, referred to as spirochetemia or bacteremia, involves systemic dissemination of disease with dermatologic manifestations and lymphadenopathy. This stage will persist for 2 to 6 weeks and is self-limiting. 70% of patients will present with hallmark skin and mucus membrane lesions. This rash usually appears as brown sores roughly the size of a penny. This rash is infectious, so any physical contact with the broken skin of an infected person may spread the infection. This maculopapular rash begins on the trunk and extends to the proximal extremities including the palms of the hands and soles of the feet in 50% of cases (7). Central nervous system (CNS) invasion will occur in 40% of patients (7, 8). In 70% of patients additional symptoms may occur including fever, malaise, weight loss, and arthralgias. It is not uncommon for patients to experience a relapse or recurrence of symptoms within 1 year. If left untreated, it may lapse into a latent stage during which the patient is no longer infectious and exhibits no clinical manifestations. The progression from primary, secondary, and latent syphilis generally takes about one year. During this time, the patient harbors replicating organisms and is infectious.

If left untreated, one-third of patients will develop tertiary syphilis (7). This stage results in progressive damage to the CNS, cardiovascular and musculoskeletal systems. Late syphilis can cause the destruction of virtually any organ or tissue including the heart, eyes, brain, nervous system, bones, and joints. One-quarter of patients will develop neurological disease, one-quarter will develop cardiovascular disease, and one-half will develop late benign gummatous syphilis (7). The gumma is the classic granulomatous inflammation which may occur to any organ.

Syphilis is of particular importance during pregnancy. According to the Centers for Disease Control and Prevention (CDC), rates of congenital syphilis in the US have mirrored rates in the general population with a slight delay of about one year (7). The risk to the fetus is present throughout the entire course of pregnancy (7). Transmission can occur not only *in utero*, but may result during delivery if the infant comes into contact with the active lesions of an infected mother. Approximately 40% of these pregnancies result in stillbirth or neonatal death (9). In untreated pregnant women with early syphilis, 70% to 100% of infants will be syphilis-infected (9). A lack of treatment can result in spontaneous abortion, stillbirth, nonimmune hydrops, preterm delivery, and perinatal death.

Diagnosis

Historically, syphilis has been commonly referred to as the "great imitator" or "great impostor" because many of the symptoms are indistinguishable from other diseases. For this reason, laboratory diagnosis is crucial. The oldest known test is the rabbit inoculation test (RIT). In this assay, rabbits are inoculated with the patient specimen and

periodically tested for development of organisms. Due to the fact that this test requires 3 months to establish a negative result, it is not used clinically and is currently only available for research purposes. Due to its inability to grow on artificial media, direct visual examination of specimens is common. Darkfield examination is used during primary and secondary stages. Samples obtained from mucocutaneous lesions are fixed to glass slides and visualized using dark-field or phase contrast microscopy. This method requires highly skilled microscopists, has a lot of variation from laboratory-to-laboratory, and even under optimal conditions has a sensitivity of only 80% (9). An alternative is direct fluorescent antibody (DFA) staining. The same type of specimen is obtained and reacted with antibodies labeled with fluorescein isothiocyanate (FITC). It is then examined using a fluorescent microscope. This method also requires highly skilled microscopists and may have variation from laboratory-to-laboratory.

Serological tests are often utilized. They can be broken down into two categories: Non-Treponemal reaginic tests and specific Treponemal tests. Nonspecific non-Treponemal reagin type antibody tests are generally used for screening purposes and include the Venereal Disease Research Laboratory test (VDRL) and the Rapid Plasma-Reagin card (RPR). These antibodies are produced against components of mammalian cells. Although they occur in patients with syphilis, they can also occur as the result of acute infections of bacteria, viruses, protozoans, autoimmune diseases, narcotic abuse, vaccinations, and pregnancy (7, 9). This cross-reactivity is known as biologic false positives. Therefore, the specificity of this assay is low. There are also well documented false negative rates of 25% to 30% in primary syphilis, 30% in latent syphilis, and 30% in late syphilis (9). Specific Treponemal tests, such as the fluorescent treponemal antibody absorption test (FTA-ABS) and the microhemagglutination test (MHA-TP) detect antibodies produced against the actual organism. They are used as confirmatory tests and to monitor response to therapy. Once positive, these tests will remain so in 85% of patients despite treatment and cure (9).

Due to the fact that 60% of chancres have atypical presentations and serological techniques have a false negative rate that varies from 20% to 36% depending upon the specific test, polymerase chain reaction (PCR) techniques offer clinicians a highly sensitive and specific alternative for the diagnosis of syphilis (7-9).

Recommendations

The US Preventive Services Task Force recommends the screening of all pregnant women and persons at increased risk of infection with syphilis. The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics recommend routine prenatal screening for syphilis at the first prenatal visit, after exposure to an infected partner, and in the third trimester for patients at high risk. The American Academy of Family Physicians and the American College of Physicians recommend serologic screening for syphilis in high-risk adults (prostitutes, persons who engage in sex with multiple partners in areas in which syphilis is prevalent, contacts of persons with active syphilis). The American Academy of Family Physicians, American Academy of Pediatrics, American Medical Association, and Bright Futures all recommend routine syphilis screening for sexually active adolescents at increased risk (12). Recommendations for the treatment and management of patients can be found in the CDC's Sexually Transmitted Diseases Summary of 2015 in Morbidity and Mortality Weekly Report (MMWR), Vol. 64 page 33-51.

Table 3. Treatment Recommendations. CDC's 2015 Sexually Transmitted Diseases Summary of 2015 CDC Treatment Guidelines Pocket Guide (20).

Recommended Regimens For Primary, Secondary or Early Latent <1 Year
Benzathine penicillin G 2.4 million units IM in a single dose
Recommended Regimens For Primary, Secondary or Early Latent <1 Year (Alternatives)
Doxycycline [a,b] 100 mg twice a day for 14 days ***OR***
Tetracycline [a,c] 500 mg orally four times a day for 14 days
Recommended Regimens For Latent > 1 Year, Latent of Unknown Durations
Benzathine penicillin G 2.4 million units IM in 3 doses each at 1 week intervals (7.2 million units total)
Recommended Regimens For Latent > 1 Year, Latent of Unknown Durations (Alternatives)
Doxycycline [a,b] 100 mg twice a day for 28 days ***OR***
Tetracycline [a,b] 500 mg orally four times a day for 28 days
Recommended Regimens For Pregnant Women
★ See complete CDC guidelines
Recommended Regimens For Neurosyphilis
Aqueous crystalline penicillin G 18–24 million units/day, administered as 3-4 million units IV every 4 hours or continuous infusion, for 10–14 days
Recommended Regimens For Neurosyphilis (Alternatives)
Procaine penicillin G 2.4 million units IM once daily ***PLUS***
Probenecid 500 mg orally four times a day, both for 10–14 days
Recommended Regimens For Congenital Syphilis
★ See complete CDC guidelines
Recommended Regimens For Children: Primary, Secondary, or Early Latent < 1 Year
Benzathine penicillin G 50,000 units/kg IM, in a single dose (maximum 2.4 million units)
Recommended Regimens For Children: Latent > 1 Year, Latent of Unknown Duration
Benzathine penicillin G 50,000 units/kg IM for 3 doses at 1 week intervals (maximum total 7.2 million units)

See CDC STD Treatment guidelines for discussion of alternative therapy in patients with penicillin allergy.

[a] If patient cannot tolerate high-dose erythromycin ethylsuccinate schedules, change to 400 mg orally 4 times a day for 14 days.

[b] Pregnant patients allergic to penicillin should be treated with penicillin after desensitization.

[c] Randomized controlled trials comparing single 2 g doses of metronidazole and tinidazole suggest that tinidazole is equivalent to, or superior to, metronidazole in achieving parasitologic cure and resolution of symptoms.

Haemophilus ducreyi

Epidemiology

Chancroid, or soft chancre, is a sexually transmitted disease caused by the bacteria *Haemophilus ducreyi*. It is the most common cause of genital ulcer diseases worldwide and is of increasing concern in the United States. The World Health Organization (WHO) estimates over 7 million cases occur annually, worldwide (13). There was a marked decrease in the number of reported incidences of chancroid in the US from 1950 to 1978. However, 1980 saw a dramatic increase to more than 5,000 reported cases (13). It is highly localized in four states California, New York, South Carolina, and Texas. In the U.S., chancroid outbreaks have been documented in New Orleans, LA, Jackson, MS, San Francisco, CA, Houston, TX, Miami, FL, Brooklyn, NY, and New York City (17). In 2002, 67 cases of chancroid were reported in the United States. South Carolina accounted for 43 (64.2%) of them (18). Chancroid is more prevalent among lower socioeconomic groups. Prostitutes are thought to be a reservoir for epidemics in North America. Risk factors associated with chancroid are the exchange of sex for money or drugs and crack cocaine use. Also a history of sex outside of the US or sex with travelers from endemic areas is significant. Chancroid is most commonly seen in uncircumcised nonwhite men (14). The fact that only 10% of reported cases occur in women may be due to asymptomatic infection (14). It is suspected that asymptomatic women may also serve as a reservoir.

Pathogenesis

The pathogenesis of *H. ducreyi* is currently poorly defined. The presence of surface lipooligosaccharide and its ability to produce a soluble cytotoxin are believed to play a role in the development of the ulcerative lesions associated with chancroid (14). Intermittent bacterial shedding has been demonstrated from lesions. This suggests that the bacteria may be transmissible and detectable before actual ulceration occurs (17). Chancroid also plays a strong role in the transmission of HIV, due to the persistent cutaneous infiltration of CD4 cells and macrophages at the site of infection (17).

Clinical Significance

The incubation period for chancroid is typically 4 to 7 days. However, it may vary from one day to several weeks. Lesions generally appear in the genital and perianal areas. They typically present as tender papules surrounded by an inflamed red halo. They progress through a pustular stage and eventually erode to form ulcers. Typically, chancroid ulcers are superficial and shallow with ragged edges. The base of the ulcer is covered with necrotic exudates, is tender, and will easily bleed. Inguinal lymphadenopathy is seen in approximately 50% of chancroid patients (2). If left untreated, it may develop into bubo formation. The bubo may rupture and form a large ulcer in the inguinal area. Bubo formation occurs in approximately 50% of cases (13).

Diagnosis

Due to the similarity in clinical presentation with other ulcerative conditions, it is crucial to utilize laboratory testing to accurately diagnose chancroid. Diagnosis of chancroid based solely on clinical grounds is often very difficult and inaccurate (14). As many as 10% of patients with chancroid are coinfected with other genital ulcer diseases such as Herpes simplex virus (HSV) or syphilis (13). Traditional laboratory detection methods often begin with gram staining techniques. Exudates from lesion or bubo aspirates are collected and smeared onto a glass slide and then stained. The slides are then analyzed microscopically for the presence of Gram-negative rods that form short chains or parallel formations often referred to as “schools of fish” or fingerprints. Due to the fact that they are often difficult to interpret and sensitivity of this method is only 50%, it is generally not recommended (13). Cultures may be performed, however, the organism can be very fastidious. This type of culture is typically not available from most general microbiology laboratories. Even when selective medium is used, sensitivity of culture is 35% to 80% (16). Although chancroid is not wide spread in the US, it is believed to be under diagnosed and under reported (17). Furthermore, the presence of chancroid is a major cofactor in the heterosexual transmission of HIV (13).

Table 4. Sensitivities for *Haemophilus ducreyi* detection tests.

Method	Sensitivity
Gram Stain	50%
Cell Culture	35% - 85%
PCR	99%

Recommendations

To circumvent the difficulty in the diagnosis of chancroid, the Centers for Disease Control and Prevention (CDC) proposes that a “probable diagnosis”, for both clinical and surveillance purposes, be made if (1) the patient has one or more painful genital ulcers, and no evidence of *Treponema pallidum* infection by dark field examination

of ulcer exudates or (2) by a serologic test for syphilis performed at least 7 days after onset of ulcers, and the clinical presentation, appearance of the genital ulcers and regional lymphadenopathy, if present, is typical for chancroid and (3) a test for Herpes simplex virus is negative. The Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases recommends the use of DNA amplification techniques such as the polymerase chain reaction (PCR) method for the detection of *H. ducreyi*, listing it as the most sensitive technique (19). Recommendations for the treatment and management of patients can be found in the CDC's Sexually Transmitted Diseases Summary of 2015 in Morbidity and Mortality Weekly Report (MMWR), Vol. 64 page 26-27.

Table 5. Treatment Recommendations. CDC's 2015 Sexually Transmitted Diseases Summary of 2015 CDC Treatment Guidelines Pocket Guide (20).

Recommended Regimens
Azithromycin 1 g orally in a single dose ***OR***
Ceftriaxone 250 mg IM in a single dose ***OR***
Ciprofloxacin 500 mg orally twice a day for 3 days ***OR***
Erythromycin base 500 mg orally three times a day for 7 days

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MEDICAL DIAGNOSTIC LABORATORIES L.L.C.

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Final

MDL#: 6198859 | ***Test Results** | **Physician Copy**

Patient Information:	**SSN:** XXX-XX-1111 **DOB:** 1/1/1987 (Age:28)	**Ordering Physician/Lab:**	**NPI:** 2121212121
Mrs.DOE, JANE M 56 LIBERTY DRIVE ABC DAYTON, NJ 08810		**JOHN DOE, MD** 202 ANY STREET DAYTON, NJ 08810	
Home: (732) 555-6666		**Tel: 609-570-1000** **Fax: 609-570-1017**	

Patient ID: **TEST123** Date Processed: **9/1/2015** Date Reported: **9/1/2015**

Test	Specimen	Date Collected / Comment	Results: Normal	Results: Abnormal	Reference/Units/Comments
Treponema pallidum (syphilis) by Real-Time PCR *	*Swab - 1*	8/31/2015 Vaginal		**Positive**	
110 Verified 9/1/2015					
Haemophilus ducreyi by Real-Time PCR *	*Swab - 1*	8/31/2015 Vaginal	**Negative**		
122 Verified 9/1/2015					
Herpes subtype (HSV-1, HSV-2) by Real-Time PCR *	*Swab - 1*	8/31/2015 Vaginal	**Negative (HSV-1)**	**Positive (HSV-2)**	**HSV-1:Negative; HSV-2:Positive;**
126 Verified 9/1/2015					

*This test was developed and its performance characteristics determined by Medical Diagnostic Laboratories, L.L.C. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

A positive result is provided for bacteria, virus, and/or fungal species when PCR amplification (real-time PCR), sequence information (Pyrosequencing), and/or sequencing analysis occurs above cut-off levels established by the laboratory. Pertinent reference intervals for the tests reported above are available from the laboratory upon request.

end of report

View:	M				
Mail:	Yes	Overnight	*Fax:*	Yes	***Manual***
	All	Yes		All	No

Medical Director, Dante A. Ragasa, MD.

PATH

MDL#: 6198859
9/1/2015
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